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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/123,212
Filing Date: April 15, 2002
Appellant(s): GODDARD ET AL.

Panpan Gao
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 9, 2005 appealing from the Office action mailed December 17, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is essentially correct, except that there is no sufficient support for appellant's assertion that the PRO1866 mRNA or polypeptide is overexpressed in tumors as compared to a normal control.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal in the brief is correct.

(7) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

*(8) **Prior Art of Record***

- Hu et al., Analysis of genomic and proteomic data using advanced literature mining. Journal of Proteome Research 2:405-412, 2003.
- Haynes et al., Proteome analysis: biological assay or data archive? Electrophoresis 19: 1862-1871, 1998.
- Wary et al., Analysis of VEGF-responsive genes involved in the activation of endothelial cells. Molecular Cancer 2:25, 2003.
- Yang et al., Vascular endothelial growth factor-induced genes in human umbilical vein endothelial cells. Arterioscler Thromb Vasc Biol 22:1797-1803, 2002.
- Young et al., U. S. Patent No. 6,525,174 B1, Feb. 25, 2003; filing date: Dec. 4, 1998.
- Stanton et al., U. S. 2002/0110804 A1, Aug. 15, 2002; 102(e) date : March 31, 2000).

The last two references cited by the Examiner are overlooked by the Appellant.

*(9) **Grounds of Rejection***

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections—35 U.S.C. § 101

(i). 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

(ii). Claims 72-79 and 82-84 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims 72-79 and 82 are drawn to an isolated polypeptide comprising SEQ ID NO: 14 and its variants, whereas claims 83 and 84 are drawn to a chimeric polypeptide comprising the polypeptide. The claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" context of use for the claimed invention which does not require further research.

The specification discloses the polypeptide of SEQ ID NO: 14 (or PRO1866), the nucleic acid of SEQ ID NO: 13 encoding the polypeptide, and antibodies against the polypeptide. Nonetheless, the instant disclosure fails to provide any sufficient information or evidence on the specific biological functions or physiological significance of the molecules of the present invention and fails to disclose a patentable utility for the claimed invention.

First, the invention lacks a well-established utility. A well-established utility is a specific, substantial, and creditable utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. The sequence and prior art search does not reveal that the polypeptide of SEQ ID NO: 14, the nucleic acid

encoding the polypeptide or an antibody that binds to the polypeptide has any well-established biological functions or any physiological significance. No art of record discloses or suggests any property or activity for the claimed molecules such that another non-asserted utility would be well-established for the claimed invention.

Secondly, the present invention does not disclose a specific and substantial utility. Table 8 of page 135 lists that the polypeptide of SEQ ID NO: 14 is significantly overexpressed in colon, lung or prostate tumors as compared to a non-cancerous human tissue control. The specification asserts that the polypeptide of the present invention is useful not only as a diagnostic marker for the presence of one or more cancerous tumors, but also serve as a therapeutic target for the tumor treatment (page 135). The Examiner notes that such an assay using microarray analysis as described in Example 30 merely measures the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO: 14. There is no sufficient information or experimental data presented on whether the polypeptide or the nucleic acid of the present invention can serve as a reliable diagnostic marker for colon, lung or prostate tumors; there is no statistical analysis of the expression data. Moreover, the assay does not establish a causative link between the polypeptide (or nucleic acid) of the present invention and colon, lung or prostate tumors. Without such critical information, one skilled in the art would not be able to use the molecule of the present invention as a diagnostic marker or as a therapeutic target for treatment of colon, lung or prostate tumors without undue experimentation. Accordingly, the results in Table 8 obtained based upon the assay

described in Example 30 only serve as the beginning point for further research on the biological functions or physiological significance of the polypeptide of SEQ ID NO: 14 or the nucleic acid encoding the polypeptide, and does not provide a specific and substantial utility for the present invention.

The specification also asserts that the nucleic acid sequences of the present invention may be used in gene therapy (the middle of page 94), the polypeptide may be employed as therapeutic agents (the middle of page 95), whereas the antibodies against the polypeptide of the present invention may be used in diagnostic assays (page 107). These asserted utilities are not specific and substantial because they do not identify or reasonably confirm a "real world" context of use. The specification fails to disclose the biological functions of the claimed molecules and any specific diseases that are associated with or can be treated with the claimed molecules. Clearly, further research would be required to identify a disease that is associated with the claimed molecules or a disease that can be treated with the claimed molecules. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

The specification further asserts numerous uses of the molecules of the present inventions. For examples, the specification asserts that the nucleotide sequences have uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA, and are useful for the preparation of a polypeptide (page

91). However, such uses are all considered research uses only designed to identify a particular function of the claimed molecules and are not a substantial utility. See, e.g., *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility."

In summary, all the asserted uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

Claim Rejections—35 U.S.C. § 112, First Paragraph, Enablement

(iii). Claims 72-79 and 82-84 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, even if the polypeptide of SEQ ID NO: 14 were to have a patentable utility, the instant disclosure would not be found to be enabling for the full scope of the invention of claims 72-76, 83, and 84.

The factors that are considered when determining whether a disclosure satisfies

enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The breadth of the claims. Claims 72-76 are drawn to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% sequence identity to the polypeptide of SEQ ID NO: 14, whereas claims 83 and 84 are drawn to a chimeric polypeptide comprising the polypeptide. Thus, the claims are broad and encompass a genus of variants of SEQ ID NO: 14. While the claims recite a limitation "wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells", such a limitation does not limit the scope of the invention in actuality because the specification does not reasonably identify or confirm that the polypeptide or the nucleic acid encoding the polypeptide is overexpressed in colon, lung or prostate tumor cells.

Nature of the invention and the state of the prior art. The present invention is related to the polypeptide of SEQ ID NO: 14, which does not have any defined biological functions or activities. The specification merely lists (Table 8 of page 135) that the polypeptide of SEQ ID NO: 14 is overexpressed in colon, lung or prostate tumors in the assay described in Example 30 without sufficient information, as noted above in the

utility rejection section. The prior art teaches two variants of the polypeptide of SEQ ID NO: 14 (U.S. Patent No. 6,525,174 B1; U.S. 2002/0110804 A1). However, the prior art does not teach that the variant of the polypeptide of SEQ ID NO: 14 is overexpressed in colon, lung or prostate tumor cells. Even if the nucleic acid of SEQ ID NO: 13 that encodes the polypeptide of SEQ ID NO: 14 were overexpressed in colon, lung or prostate tumor cells, the polypeptide of SEQ ID NO: 14 would not necessarily be overexpressed in colon, lung or prostate tumor cells because there is no correlative link established between the nucleic acid expression and the level of the polypeptide. The prior art teaches that the multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts (see, e.g., Haynes et al., Electrophoresis 19: 1862-1871, 1998, bottom of left column of page 1870).

The amount of direction or guidance presented and the existence of working examples. Other than the polypeptide set forth in SEQ ID NO: 14, the specification fails to provide sufficient direction and/or working example on how to make those variants and homologues that have the same function as that of the polypeptide of SEQ ID NO: 14 and on how to use those variants and homologues that do not have the same activity as that of the polypeptide of SEQ ID NO: 14. There are no examples of functional variants and homologues of SEQ ID NO: 14. While Figure 14 discloses the full-length polypeptide of SEQ ID NO: 14, the specification is silent with respect to which residues

may be altered without loss of activity. The instant disclosure does not show (i) which portions of the polypeptide of SEQ ID NO: 14 are critical to its activity; and (ii) what modifications (e.g., substitutions, deletions or additions) one can make to SEQ ID NO: 14 will result in a mutant or a fragment with the same functions as that of the polypeptide set forth in SEQ ID NO: 14.

The relative skill of those in the art, the predictability or unpredictability of the art, and the quantity of experimentation necessary. While the level of skill in the DNA recombination technology is relatively high, the microarray analysis has been widely used to determine the gene expression levels (Yang et al., Arterioscler Thromb Vasc Biol 22:1797-1803, 2002u et al., Journal of Proteome Research 2:405-412, 2003), the art does not teach that if a single polypeptide or a nucleic acid is overexpressed in a certain type of tumor as compared with a normal control, such as colon, lung or prostate tumors, variants of the polypeptide or nucleic acid will necessarily be overexpressed in the tumor. Procedures for making variants of SEQ ID NO: 14 which have at least 80% identity to SEQ ID NO: 14 and retains its recited activity are not conventional in the prior art. It is unpredictable whether a variant of SEQ ID NO: 14 would retain the same function as that of the full length of polypeptide of SEQ ID NO: 14. Thus, due to lack of the disclosure of the functions of encompassed polypeptides structurally related to SEQ ID NO: 14, sufficient guidance and/or working examples provided in the specification, and teachings in the art on how to use those variants of the polypeptide of SEQ ID NO: 14, it would take undue experimentation for one skilled in the art to make and use the

variants of the polypeptide of SEQ ID NO: 14.

Accordingly, even if the polypeptide of SEQ ID NO: 14 were to have a patentable utility, the instant disclosure would not be found to be enabling for the genus of polypeptides encompassed by the instant claims. Thus, it would require undue experimentation for one skilled in the art to make and use the claimed invention commensurate in scope with the claims.

Claim Rejections—35 U.S.C. § 112, First Paragraph, Written Description

(iii). The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(iv). Claims 72-76, 83, and 84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics,

structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 72-76 are drawn to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% sequence identity to the polypeptide of SEQ ID NO: 14, whereas claims 83 and 84 are drawn to a chimeric polypeptide comprising the polypeptide. The claims do not require that the polypeptide possess any particular conserved structure nor other disclosed distinguishing feature. While the claims recite a limitation "wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells", such a limitation does not limit the scope of the invention in actuality because the specification does not reasonably identify or confirm that the polypeptide or the nucleic acid encoding the polypeptide is overexpressed in colon, lung or prostate tumor cells. Thus, the claims are drawn to a genus of polypeptides that is defined only by a partial structure in the form of a recitation of percent identity.

The instant disclosure of an isolated polypeptide of SEQ ID NO: 14 and its encoding nucleic acid molecule set forth in SEQ ID NO: 13 does not adequately support the scope of the claimed genus, which encompasses a substantial variety of homologues or variants of the polypeptide of SEQ ID NO: 14. A description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the

genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). While disclosing the amino acid sequence of SEQ ID NO: 14 (Figure 14), the instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Moreover, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In the instant case, only one polypeptide sequence has been identified with *a potential link* to colon, lung or prostate tumors. No other species have been disclosed. One species is not adequately representative of the many sequences encompassed by the claims.

Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed polypeptides as being identical to those instantly claimed.

Due to the breadth of the claimed genus and lack of the definitive structural or functional features of the claimed genus, one skilled in the art would not recognize from the disclosure that the Appellant was in possession of the claimed genus. Accordingly, only

the isolated polypeptide comprising SEQ ID NO: 14 (and its mature form, i.e., lacking the signal peptide sequence), but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections—35 U.S.C. § 102 (e)

(v). The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(vi). Claims 72-74, 83, and 84 are rejected under 35 U.S.C. 102(e) as being anticipated by Young et al. (U.S. Patent No. 6,525,174 B1, Feb. 25, 2003; filing date: Dec. 4, 1998).

Young et al. teach a polypeptide that shares 92.5% sequence identity with SEQ ID NO: 14. Young et al. further teach a fusion protein comprising the polypeptide and an epitope tag, such as His-tag, HA-tag (Example 9; column 286). The art is silent regarding the cited functional limitation in the instant claims. However, all that appears to be necessary to achieve the cited functional limitation is the recited structural limitation which the art shares. Thus, the reference of Young et al. meets the limitations of claims 72-74, 83, and 84.

(vii). Claims 72-75, 83, and 84 are rejected under 35 U.S.C. 102(e) as being anticipated by Stanton et al. (U.S. 2002/0110804 A1, Aug. 15, 2002; 102 (e) date: March 31, 2000). Stanton et al. teach a polypeptide that shares 96.7% sequence identity with SEQ ID NO: 14. Stanton et al. further teach a fusion protein comprising the polypeptide and an immunoglobulin constant region (an Fc region; see [0197]). The art is silent regarding the cited functional limitation in the instant claims. However, all that appears to be necessary to achieve the cited functional limitation is the recited structural limitation which the art shares. Thus, the reference of Stanton et al. meets the limitations of claims 72-75, 83, and 84.

(10) Response to Argument

I. Rejection of claims 72-79 and 82-84 under the utility requirement of 35 USC §101

From the bottom of page 9 to the middle of page 12 of the Brief, Appellant, citing case law and MPEP, reviews the legal standard for utility, with which the Examiner takes no issue.

Beginning at page 12 of the Brief, Appellant argues that the microarray data disclosed in Example 30 establishes a credible, substantial and specific patentable utility for the PRO1866 polypeptide. Appellant argues that Example 30 and Table 8 explicitly states that PRO1866 is significantly overexpressed in colon, lung or prostate tumors as compared to the universal normal control. Appellant argues that the PRO1866 polypeptides are useful not only as diagnostic markers for the presence of one or more

cancerous tumors, but also serve as therapeutic targets for the treatment of those tumors.

Appellant's argument has been fully considered, but is not deemed to be persuasive for the following reasons. An assay using microarray analysis as described in Example 30 is essentially a hybridization assay. The only difference between microarray analysis and a simple hybridization is that a nucleic acid microarray often contains thousands of gene sequences. Thus, the microarray analysis merely measures the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO: 14. There is no evidence regarding whether the level of PRO1866 polypeptide of SEQ ID NO: 14 or, even more broadly, its variants significantly increased in colon, lung or prostate tumor samples in comparison with the normal control. There is no sufficient information or experimental data presented on whether the polypeptide or the nucleic acid of the present invention can serve as a reliable diagnostic marker for colon, lung or prostate tumors; there is no statistical analysis of the expression data. Moreover, the assay does not establish a causative link between the polypeptide (or nucleic acid) of the present invention and colon, lung or prostate tumors. Without such critical information, one skilled in the art would not be able to use the polypeptide of the present invention as a therapeutic target for treatment of colon, lung or prostate tumors without undue experimentation. The information disclosed in the instant specification is preliminary at best. Clearly further research would be required to determine whether the PRO1866 polypeptide can serve as a reliable diagnostic marker for colon, lung or prostate tumors

or as a therapeutic target for treatment of colon, lung or prostate tumors. Accordingly the claimed utility is not substantial.

The instant situation is analogous to what was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct, 1966), where the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an application to engross what may prove to be a broad field", and "a patent is not a hunting license", "[it] is not a reward for the search, but compensation for its successful conclusion."

Beginning at the middle of page 13 of the Brief, Appellant, citing a statement from Dr. Smith's declaration, argues that the mRNA encoding PRO1866 shows significant overexpression in colon, lung or prostate tumors as compared to the universal normal control. Appellant argues that based upon the declaration by Dr. Smith and the teachings in the specification, one of ordinary skill would find it credible that the PRO1866 polypeptides of the present invention are useful as diagnostic markers for the presence of those colon, lung or prostate tumors.

Appellant's argument has been fully considered, but is not deemed to be persuasive for the reasons set forth immediately above. In addition, the declaration by Dr Smith states that molecules identified as being detectably overexpressed in a human tumor of epithelial origin as compared to the universal normal control are useful as diagnostic markers for the determination of the presence of that particular type of human tumor. However, Appellant concludes that the PRO1866 polypeptides are useful as diagnostic markers for colon, lung or prostate tumors. In doing so, the Examiner believes that Appellant's reasoning is flawed logically and does not account for a gap between a gene expression level and a protein level. The molecule detected by the microarray was one specific mRNA that is complementary to the nucleic acid of SEQ ID NO: 13 and encodes the polypeptide of SEQ ID NO: 14, not the polypeptide of SEQ ID NO: 14, not the variants of the polypeptide of SEQ ID NO: 14. There is no correlative link established between the level of gene expression and the level of the protein in general (see below for details).

Beginning at the 2nd paragraphs of page 14 of the Brief, Appellant criticizes a statement from the final rejection and argues that the diagnostic utility asserted in the present application is to be able to ***quantitatively*** compare the level of PRO1866 expression in a tumor sample to a normal control sample and to detect a ***relative*** difference in the level of PRO1866 expression between the tumor and normal samples.

Appellant's argument has been fully considered, but is not deemed to be persuasive because while listing merely PRO1866 molecule as being overexpressed in colon, lung or prostate tumors (Table 8 at page 135), the specification fails to provide either the actual level or the relative degree of the expression of PRO1866 polypeptide of SEQ ID NO: 14 or its encoding nucleic acid. There is no statistical analysis or validation analysis of the expression data. Numerous questions remain to be answered: such as how many tumor samples and normal control samples were used in the study? How were the normal control samples pooled? What types of colon, lung or prostate tumor samples were utilized in the assay (there are different types of lung tumors, for example)? What were the actual level or relative degree of expression of the protein or the nucleic acid encoding the polypeptide in the universal control versus the tumor samples? How to distinguish a truly positive hybridization signal from a false one? How many fold difference in the expression level between a tumor sample and a normal control was considered as being significant? Without such critical information, how would one of skill in the art be able to quantitatively compare the level of PRO1866 expression in a tumor sample to a normal control sample and to detect a relative difference in the level of PRO1866 expression between the tumor and normal samples?

Beginning at the 2nd paragraph of page 15 of the Brief, Appellant submits that the Examiner has overlooked the ample information provided in Example 30 for determining whether a gene is significantly overexpressed. In particular, the specification at page 134 offers ample information on how to ascertain the "cutoff ratio" for hybridization.

Appellant further submits the specification provides very clear guidelines as to how high levels must be to be deemed "significant".

Appellant's argument has been fully considered, but is not deemed to be persuasive because the specification discloses that if the hybridization signal of a probe from a test (disease tissue) sample is greater than hybridization signal of probe from control (normal tissue) sample, the gene or genes overexpressed in the disease are identified (lines 22-24 of page 134). The specification fails to disclose the specific "cutoff ratio". Is the "cutoff ratio" 1-fold, 5-fold, 10-fold, or 100-fold difference? The art cautions researchers from drawing conclusions based upon small changes in transcription levels between normal and cancerous tissue. For example, Hu et al. analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (Journal of Proteome Research 2:405-412, 2003). Hu et al. teach that there was no evidence of a correlation between altered gene expression and a known role in the disease for genes displaying a 5-fold change or less in tumors compared to normal. On the other side, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see, e.g., Abstract). If the "cutoff ratio" were disclosed in the specification to be 100-fold, for example, the nucleic acid of SEQ ID NO: 13 that encodes the PRO1866 polypeptide would likely to have a specific and substantial utility as a diagnostic marker for colon, lung or prostate tumors. However, it is not the case here. Most importantly, an assay

using microarray analysis as described in Example 30 merely measures the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO: 14 or its variants.

Beginning at the bottom of page 15 of the Brief, Appellant submits that Example 30 explicitly states that the PRO1866 mRNA and polypeptide are significantly overexpressed in colon, lung or prostate tumors as compared to the universal normal control. Appellant submits that Appellant should not be required to disclose the experimental details as long as Appellants provide the data showing that PRO1866 is significantly overexpressed in colon, lung or prostate tumors. Appellant further submits that the Examiner has not provided any evidence that one ordinary skilled in the art would doubt the credibility of the data in Example 30.

Appellant's argument has been fully considered, but is not deemed to be persuasive for the reasons set forth above.

At the 2nd paragraph of page 17 of the Brief, Appellant submits that the instant disclosure indicated that the experimental results disclosed in Table 8 of Example 30 are based upon reliable experimental design and solid statistical analysis.

Appellant's argument has been fully considered, but is not deemed to be persuasive because regardless how the experiments were designed, the specification simply fails

to disclose sufficient information to establish a specific and substantial utility for the claimed subject matter, as noted above.

At the 3rd paragraph of page 17 of the Brief, Appellant argues that Appellant merely claims that the observed and herein described differential expression profile of PRO1866 is diagnostic for the presence of only those colon, lung or prostate tumors that exhibit significant overexpression of PRO1866 as compared to the corresponding and respective normal tissue type or the universal control. Appellant submits that Appellant is not asserting a general diagnostic utility for the entire class of all human lung tumors, all human colon tumors, or all human prostate tumors, there is no need to demonstrate statistical significance across a wide range of different tumor types.

Appellant's argument has been fully considered, but is not deemed to be persuasive. First, Appellant's argument is a "circular" argument—PRO1866 is diagnostic for those colon, lung or prostate tumors that exhibit significant overexpression of PRO1866. It does not identify the specific type of tumor that can be diagnosed. Secondly, statistical analysis and validation analysis are needed to establish a marker for diagnosis of a certain type of tumor, for example, lung adenocarcinomas. A sufficient sample size (i.e., number of tumor samples and healthy control samples) is required for assessment of the difference in the expression level of a gene or protein at a given significance level (e.g., $P<0.01$). Without such an analysis, one of skill in the art would not be able to

judge whether a nucleic acid or a protein can be practically used as a diagnostic marker for a specific type of tumor.

Beginning at the bottom of page 17 of the Brief, Appellant argues that a prima facie case of lack of utility has not been established. Appellant submits that it is not a legal requirement to establish that increased mRNA expression "necessarily results in increased expression at the polypeptide level, or that protein levels can be accurately predicted. Appellant submits that the law requires only that one skilled in the art should accept that such a correlation is more likely than not to exist. Appellant argues that Haynes teaches that there was a general trend but no strong correlation between protein and transcript levels and there is a positive correlation between mRNA and protein amongst most of the 80 yeast proteins studied.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, 35 U.S.C.§ 101 requires disclosure of a specific and substantial utility that is particular to the subject matter claimed and that identifies a "real world" context of use for the claimed invention without further research. In the instant case, there is no sufficient evidence on the record, either from the instant disclosure, Appellant's declaration or the prior art, which would reasonably identify or confirm the use of the polypeptide of SEQ ID NO: 14 and its variants as a diagnostic marker for colon, lung or prostate tumors. There is no sufficient evidence supporting Appellant's

assertion that it is more likely than not that the polypeptide of SEQ ID NO: 14 and its variants are overexpressed in colon, lung or prostate tumors.

Secondly, Appellant ignores the overall teachings of Haynes et al. At 2nd paragraph of left column of page 1863, Haynes et al. clearly states, "For some genes studied equivalent mRNA transcript level translated into protein abundances which varied by more than 50-fold. Similarly, equivalent steady state protein expression levels were maintained by transcript levels varying by as much as 40-fold". Clearly, Appellant's argument that a positive correlation exists between mRNA and protein is not true. Moreover, Haynes et al. conclude "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (bottom of left column of page 1870). Accordingly, the limited disclosure in the instant case does not meet the legal standard for a specific and substantial utility required under 35 U.S.C.§ 101.

Beginning at the 2nd paragraph of page 19 of the Brief, Appellant criticizes the publication of Hu et al. and claims that Hu et al. use different statistical methods to manipulate various aspects of the input data to affect the outcome, citing a statement from the article (4th paragraph of right column of page 406) as evidence.

Appellant' argument has been fully considered, but is not deemed to be persuasive because Hu et al. analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (Journal of Proteome Research 2:405-412, 2003). Hu et al. teach that there was no evidence of a correlation between altered gene expression and a known role in the disease for genes displaying a 5-fold change or less in tumors compared to normal. On the other side, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see, e.g., Abstract). Hu et al. listed systematic sources of false positives and false negatives in Table 1. Removing the false positives and false negatives would make the study more meaningful. For example, the false positive caused by gene symbol/name that is not unique is eliminated (see Table 1). This can only validate the data analysis, which is acceptable in the art as judged by the fact that the publication is a peer-reviewed article and cannot be said to be "manipulation of data to affect the outcome".

At the top of page 20 of the Brief, Appellant argues that the statistical analysis is not a reliable standard because the frequency of citation only reflects the current research interest in a molecule, not the true biological function of the molecule. Appellant also submits that it often happens in a scientific study that important molecules are overlooked by the scientific society for many years until the discovery of their true function.

Appellant' argument has been fully considered, but is not deemed to be persuasive because Hu et al. comprehensively summarize and estimates the relative strengths of all human gene-disease relationship in Medline, and analyzed a microarray expression dataset comparing breast cancer and normal breast tissue in the context of existing knowledge (see, e.g., Abstract). While it is true that "relationship established by frequency of co-citation do not necessarily represent a true biological link", as Hu et al. stated, "it is strong evidence to support a true relationship" (1st paragraph of right column of page 411). Further, while some functional molecules are not included in the analysis, a sample size of 2286 genes is sufficient to validate author's conclusion. The purpose of a statistical analysis is to predict the property or behavior of the overall population based upon analysis of a sample of the population.

At the 3rd paragraph of page 26 of the Brief, Appellant argues that the conclusion in Hu et al. only applies to a specific type of breast tumor (estrogen receptor-positive breast tumor) and cannot be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the following reasons. Hu et al. teach that their study has two implications. First, a careful hunt for corroborating evidence of a role in breast cancer should precede any further study of genes with less than 5-fold expression level change. Second, any genes with 10-fold changes or more are likely to related to breast cancer and warrant attention

(2nd paragraph of left column of page 412). Hu et al. teach that it is likely that this threshold will change depending on the disease as well as the experiment (2nd paragraph of left column of page 412). These teachings caution researchers from drawing conclusions based upon small changes in transcription levels between normal and cancerous tissue. Hu et al. clearly states: "it is not uncommon to see expression changes in microarray experiment as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful" (bottom of right column of page 411). Hu et al. further states: "in any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (1st paragraph of left column of page 405).

Accordingly, in view of the limited disclosure in the instant case—lack of disclosure of the "cut-off ratio" that was used to determine whether a hybridization signal was significant, lack of the statistical analysis, lack of the validation of universal normal control, and lack of establishment of a correlative link between gene expression and protein level or a causal link between gene expression and colon, lung or prostate tumours, the teachings of Hu et al. support the Examiner's position that further research is needed to reasonably identify or confirm a specific and substantial utility for the instantly claimed polypeptide of SEQ ID NO: 14 and its variants.

Beginning at the 2nd paragraph of page 21 of the Brief, Appellant argues that it is more likely than not for increased mRNA levels to predict increased protein levels. Appellant presents a declaration by Dr. Polakis under 37 CFR 1.132 as evidence that mRNA expression correlates well with protein levels in general. Appellant submits that while the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Dr. Polakis declaration greatly exceed this legal standard. In the declaration, Dr. Polakis states that a primary focus of the tumor antigen project is to identify tumor cell markers useful as targets for diagnosis and treatment of cancer in humans. Dr. Polakis states that a variety of scientific techniques, including microarray analysis, have been used for detecting and studying differential gene expression in human tumor cells relative to normal cells at genomic DNA, mRNA, and protein levels. Dr. Polakis states that approximately 200 genes transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states antibodies to about 30 of the tumor antigen proteins have been developed and used to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Dr. Polakis states approximately 80% samples show correlation between increased mRNA levels and changes in the level of protein expressed from that mRNA. Dr. Polakis states that it remains a central dogma in molecular biology that increased RNA levels are predictive of corresponding increased levels of the encoded protein. Dr.

Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule.

The declaration of Dr. Polakis is insufficient to overcome the rejection of claims 72-79 and 82-84 under 35 U.S.C.§101 and Appellant's argument is not deemed to be persuasive for the following reasons. First of all, it is important to note that Dr. Polakis clearly states that a variety of scientific techniques, including microarray analysis, have been used for detecting and studying differential gene expression in human tumor cells relative to normal cells at genomic DNA, mRNA, and protein levels. Dr. Polakis does not state that microarray analysis *alone* can establish the use of a polypeptide as a diagnostic marker for a specific tumor. In fact, the art teaches the results obtained from microarray analysis require confirmation by independent methods, such as northern blot analysis and Western blot analysis (see, e.g., Wary et al., Molecular Cancer 2:25, 2003; Yang et al., Arterioscler Thromb Vasc Biol 22:1797-1803, 2002). Secondly, Dr. Polakis states approximately 80% samples show correlation between increased mRNA levels and *changes in the level of protein* expressed from that mRNA. However, Dr. Polakis does not state whether the increase in protein level was significant enough to be meaningful as being a diagnostic marker for colon, lung or prostate tumors.

Thirdly, Dr. Polakis states that approximately 200 genes transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis does not state that how many proteins encoded by the 200 genes are

expressed at significantly higher levels than in corresponding normal human cells. Dr. Polakis states antibodies to about 30 of the tumor antigen proteins have been developed and used to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Dr. Polakis does not state that the 30 of "tumor antigen proteins" are expressed at significantly higher levels than in corresponding normal human cells.

Moreover, the declaration does not provide data such that the Examiner can independently analyze and draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoding polypeptide. In fact, the art teaches the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (Haynes et al., Electrophoresis, 19:1862-1871, 1998; see, left column of page 1863; Figure 1). While the absolute certainty is not the legal standard for utility, a specific and substantial utility in reasonably confirmed and practical form is required for the claimed invention.

Furthermore, the specification provides no information regarding the specific degrees of the increase in mRNA level or protein levels of PRO1866 in tumor tissues relative to corresponding normal tissues. There is no statistical analysis of the expression data. For example, there is no disclosure of the number of tumor samples and control

samples that were analyzed, which is clearly required for the establishment of a reliable diagnostic marker for colon, lung or prostate tumors. The specification merely discloses that if the hybridization signal of a probe from a test (disease tissue) sample is greater than hybridization signal of probe from control (normal tissue) sample, the gene or genes overexpressed in the disease are identified (lines 22-24 of page 134). The art cautions researchers from drawing conclusions based upon small changes in transcription levels between normal and cancerous tissue, as noted above.

Beginning at the bottom of page 22 of the Brief, Appellant argues that the Examiner has also misunderstood the teachings in Wary et al. and Yang et al. and therefore has reached an incorrect conclusion that the art teaches that results obtained from microarray analysis require confirmation by independent methods. Appellant submits that Wary et al. and Yang et al. simply further tested the protein or mRNA expression of the identified genes in the microarray analysis with other techniques available in the art, such as Northern blot and Western blot.

Appellant's argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, the examiner's position is in agreement with the declaration of Dr. Polakis et al., who clearly state that a variety of scientific techniques, including microarray analysis, have been used for detecting and studying differential gene expression in human tumor cells relative to normal cells at genomic DNA, mRNA, and protein levels. Dr. Polakis does not state that microarray analysis alone can establish

the use of a polypeptide as a diagnostic marker for a specific tumor. Secondly, the cited art explicitly teaches that results obtained from microarray analysis require confirmation by independent methods. For example, at 2nd paragraph of right column of page 1799, Yang et al. clearly states, "To validate the gene expression data by a second, more sensitive, quantitative, and independent method, we analyzed the expression of 12 of the identified genes...". In another cited publication (Journal of Proteome Research, 2:405-412, 2003), Hu et al. teach "in any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (1st paragraph of left column of page 405). There would be no logical rational for authors of the cited papers to perform additional assays if microarray alone can reasonably identify or confirm the use of a polypeptide or a nucleic acid as a diagnostic marker for a specific tumor or a therapeutic target.

Beginning at the 3rd paragraph of page 23 of the Brief, Appellant criticizes examiner's analysis of Declaration of Dr. Polakis and argues that Dr. Polakis's declaration is not merely conclusive and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art. Appellant further submits that this rejection is improper under both the case law and the utility guidelines. Appellant' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth above.

Beginning at page 25 of the Brief, Appellant presents a declaration from Dr. Smith as the evidence that the universal normal control is a well-accepted, informative, and reliable control. Dr. Smith states that molecules identified as being detectably overexpressed in a human tumor of epithelial origin as compared to the universal normal control sample are useful as diagnostic markers for the determination of the presence of that particular type of human tumor.

The declaration by Dr. Smith is insufficient to overcome the rejection of claims 72-79 and 82-84 under 35 U.S.C. §101 for the following reasons. First of all, the declaration does not provide evidence or data such that the Examiner can independently analyze and draw conclusions. Only Dr. Smith's opinions are provided in the declaration. There is no evidentiary support to Dr. Smith's statement that molecules identified as being detectably overexpressed in a human tumor of epithelial origin as compared to the universal normal control sample are useful as diagnostic markers for the determination of the presence of that particular type of human tumor. There is no art support for Appellant's assertion that the universal normal control is a well-accepted, informative, and reliable control.

Dr. Smith states: "Microarray analysis performed in my laboratory have confirmed the general *correlation* in overall gene expression profiles between (i) the universal normal control sample and (ii) individual normal non-cancerous human tissue samples of epithelial origin". However, such a statement does not indicate how well the universal

control reflects the actual gene expression level in each of pooled tissues. How many normal human tissues samples of epithelial origin were pooled? How were the normal control samples pooled? What were the expression levels in each of pooled normal tissues? The fact that the pooled normal control samples were used implies, by itself, variation of the gene expression levels in each of pooled normal tissues; otherwise, if the gene expression levels in all normal control tissues of epithelial origin were identical or very similar, there would no need to use the pooled universal control. Unfortunately, the declaration of Dr. Smith does not provide any information or evidence that could be used to address any of these issues.

Dr. Smith states: "microarray analysis actually performed in my laboratory have shown that when molecules are identified as being overexpressed in a human tumor sample of epithelial origin relative to the universal normal control sample, in a majority of cases, that molecule is also confirmed as being overexpressed in the human tumor tissue sample relative to its normal human tissue counterpart". However, Dr. Smith does not say how "a majority of cases" is defined. Does the "majority" mean 50.1% of all cases or 99% of all cases? If 99% of all cases were confirmed, the nucleic acid would *likely* to have a specific and substantial utility as a diagnostic marker for a certain tumor; on the other hand, if only 50.1% of all cases were confirmed, the utility of the nucleic acid is not substantial. After all, Dr. Smith's declaration shows that the microarray cannot rule out the false positive results and the results based upon microarray analysis need to be confirmed.

Moreover, the declaration by Dr. Smith addresses one specific issue, the normal tissue control; it does not establish the use of the PRO1866 polypeptide as a diagnostic marker for colon, lung or prostate tumors. Even if the universal normal control were a well-accepted, informative, and reliable control, the limited disclosure would still not be found to provide a specific and substantial utility for the polypeptide of SEQ ID NO: 14 and its variants for the reasons set forth at pages 16-19 above. Thus, the utility rejection must be held.

At the top of page 28 of the Brief, Appellant concludes this section by stating that the instant specification discloses a specific, credible and substantial utility for the PRO1866 polypeptide as a diagnostic marker for colon, lung or prostate tumors. The Examiner believes that the rejections should be sustained for the reasons set forth above.

II. Rejection of claims 72-79 and 82-84 under 35 USC § 112, 1st paragraph, enablement

Claims 72-79 and 82-84 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Appellant refers to the arguments and information presented in response to the rejection under 35 U.S.C. § 101. Appellant submits that the PRO1866 polypeptides have utility in

the diagnosis of cancer. The Examiner believes that the rejection should be sustained for the reasons set forth above.

Beginning at the bottom of page 28 of the Brief, Appellant responds to the issue related to the scope of enablement, which is set forth on the assumption that the claimed invention has a specific and substantial utility. Appellant argues that the claimed variants all share the functional limitation that "the nucleic acid encoding said polypeptide is overexpressed in colon, lung, or prostate tumor cells" and Example 30 of the present application provides a step-by-step guidelines and protocols for microarrays. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO1866 protein is overexpressed in colon, lung or prostate tumor cells, and therefore falls within the parameters of the claimed invention. Appellant further submit that the specification describes methods for the determination of percent identity between two amino acid sequences and provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity. Appellant submits that one of ordinary skill in the art has a sufficient high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO: 14.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, while the claims recite a limitation "wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells", such

a limitation does not limit the scope of the invention in actuality because the specification does not reasonably identify or confirm that the polypeptide or the nucleic acid encoding the polypeptide is overexpressed in colon, lung or prostate tumor cells. Secondly, the microarray analysis disclosed in Example 30 merely measures the mRNA level, does not measure the level of a polypeptide, as noted above. Thirdly, a method of calculating the percentage identity is not equivalent to a method of making and it does not provide sufficient guidance on how to make the functional variants of the polypeptide of SEQ ID NO: 14.

Furthermore, Appellant's argument that the specification provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity is simply incorrect. The functional activity recited in the instant claims is "wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung, or prostate tumor cells". Nowhere does the specification provide guidance as to changes that may be made to a PRO polypeptide without adversely affecting such a recited activity. Procedures for making variants of SEQ ID NO: 14 which have at least 80% identity to SEQ ID NO: 14 and retains its recited activity are not conventional in the prior art because the prior art does not teach that it is predictable that a variant of polypeptide or a nucleic acid will be necessarily overexpressed if a single polypeptide or nucleic acid is overexpressed in a certain type of tumor as compared with a normal control, such as colon, lung or prostate tumors.

Accordingly, even if the polypeptide of SEQ ID NO: 14 were to have a patentable utility, the instant disclosure would not be found to be enabling for the genus of polypeptides encompassed by the instant claims. It would require undue experimentation for one skilled in the art to make and use the claimed invention commensurate in scope with the claims.

At the 2nd paragraph of page 30 of the Brief, Appellant argues that a considerable amount of experimentation is permissible, if it is merely routine. Appellants further submits that the identification of variant PRO1866 polypeptides having 80% identity to SEQ ID NO: 14, wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells, can be performed by techniques that were well known in the art, and that the performance of such work does not require undue experimentation. Appellant' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth immediately above.

At the 3rd paragraph of page 30 of the Brief, Appellant concludes this section by urging that the rejection of claims 72-79 and 82-84 under 35 U.S.C. § 112, first paragraph be reversed. The Examiner believes that the rejections should be sustained for the reasons set forth above.

III. Rejection of claims 72-76, 83, and 84 under 35 USC § 112, 1st paragraph, written description

Claims 72-76, 83, and 84 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Beginning at page 31 of the Brief, Appellant, citing case law, reviews the legal standard for written description, with which the Examiner takes no issue.

At the 2nd paragraph of page 32 of the Brief, Appellant submits that the instant specification evidences the actual reduction to practice of the amino acid sequence of SEQ ID NO: 14. Thus, the genus of the polypeptides with at least 80% sequence identity to SEQ ID NO: 14, whose encoding nucleic acids possess the functional property of being overexpressed in colon, lung or prostate tumor cells, would meet the requirement of 35 U.S.C.§ 112, first paragraph as providing adequate written description.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the following reasons. While the specification provides an adequate written description for the PRO1866 polypeptide of SEQ ID NO: 14 (and its mature form, i.e., lacking the signal peptide sequence), it fails to provide adequate written description for its variants or homologues because the polypeptide of SEQ ID NO: 14 is not representative species of the claimed genus. The recited functional limitation, "wherein the nucleic acid

encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells", does not limit the scope of the invention because the specification does not provide sufficient evidence showing that the polypeptide of SEQ ID NO: 14, let alone its variants, is overexpressed in colon, lung or prostate tumor cells and can be used as a reliable diagnostic marker for colon, lung or prostate tumors. As noted in the utility rejection section, the cited prior art also teaches against the likelihood that the single species of SEQ ID NO: 14 is reduced to practice by disclosing its complete structure. Therefore, the instant disclosure fails to evidence the actual reduction to practice of the amino acid sequence of SEQ ID NO: 14, let alone its variants.

From the 3rd paragraph of page 32 of the Brief, Appellant disagrees with the Examiner's opinion that only one polypeptide sequence has been identified with a potential link to cancer as recited in the claims. Appellant submits that the inventor is not required to describe every single detail of his invention. Appellant further argues that the present invention is from the field of recombinant DNA technology, it is well established that the level of skill in this field is relatively high and the teachings imparted in the specification must be evaluated through the eyes of a highly skilled in the artisan as of the date the invention was made.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the following reasons. The Examiner agrees that compliance with the written description requirement does not require that the inventor describe every single detail of his

invention. However, the description has to satisfy the description requirement by, for example, providing representative species of the claimed genus or the structural and functional characteristic of the claimed genus. In the instant case, the specification merely discloses a single species, the polypeptide of SEQ ID NO: 14, fails to disclose any specific biological functions or any physiological significance of the claimed genus, and fails to disclose the conserved regions that are critical to the functions of the claimed genus and methods of making the claimed genus of variants of the polypeptide of SEQ ID NO: 14. The specification does not provide sufficient evidence showing that the polypeptide of SEQ ID NO: 14 and its variants are overexpressed in colon, lung or prostate tumor cells, as noted in the utility rejection section.

While the level of skill in the DNA recombination technology is relatively high, the microarray analysis has been widely used to determine the gene expression levels as demonstrated by the cited publications, the art does not teach that if a single polypeptide or a nucleic acid is overexpressed in a certain type of tumor as compared with a normal control, such as colon, lung or prostate tumors, variants of the polypeptide or nucleic acid will necessarily be overexpressed in the tumor.

At the 1st paragraph of page 33 of the Brief, Appellant submits that Example 30 of the present application provides a step-by-step guidelines and protocols for microarrays. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO1866 protein or its mRNA is overexpressed in colon, lung or prostate

tumor cells, and therefore falls within the parameters of the claimed invention. Appellant further submit that the specification describes methods for the determination of percent identity between two amino acid sequences and provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, the microarray analysis disclosed in Example 30 merely measures the mRNA level, does not measure the level of a polypeptide, as noted above. Second, a method of calculating the percentage identity is not equivalent to a method of making and it does not provide description for the instantly genus of PRO1866 polypeptide variants. Moreover, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In the instant case, only one polypeptide sequence has been identified with a potential link to colon, lung or prostate tumors. No other species have been disclosed. One species is not adequately representative of the many sequences encompassed by the claims.

Furthermore, Appellant's argument that the specification provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity is simply incorrect. The functional activity recited in the instant claims is "wherein

the nucleic acid encoding said polypeptide is overexpressed in colon, lung, or prostate tumor cells". Nowhere does the specification provide guidance as to changes that may be made to a PRO polypeptide without adversely affecting such a recited activity. Procedures for making variants of SEQ ID NO: 14 which have at least 80% identity to SEQ ID NO: 14 and retains its activity are not conventional in the art because the prior art does not teach that if a single polypeptide or nucleic acid is overexpressed in a certain type of tumor as compared with a normal control, such as colon, lung or prostate tumors, its variants will necessarily be overexpressed.

At the 2nd paragraph of page 33 of the Brief, Appellant argues that Appellants have recited structural features, namely 80% sequence identity to SEQ ID NO: 14, which are common to the genus. Appellant also argues that appellant has also provided guidance as to how to make the recited variants of SEQ ID NO: 14, including listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth above. Moreover, the recited sequence percent identity does not represent an effective structural limitation because it says nothing about the conserved structure or the distinguishing feature of the genus, or the relation of structure to function.

From the bottom of page 33 the Brief, Appellant concludes this section by urging that the rejection of claims72-76, 83, and 84 under 35 U.S.C. § 112, first paragraph for written description be reversed. The Examiner believes that the rejections should be sustained for the reasons set forth above.

IV. Rejection of claims 72-75, 83, and 84 under 35 USC § 102 (e)

Claims 72-74, 83, and 84 are rejected under 35 U.S.C. 102(e) as being anticipated by Young et al. (U.S. Patent No. 6,525,174 B1, Feb. 25, 2003; filing date: Dec. 4, 1998).

Claims 72-75, 83, and 84 are rejected under 35 U.S.C. 102(e) as being anticipated by Stanton et al. (U.S. 2002/0110804 A1, Aug. 15, 2002; 102 (e) date: March 31, 2000).

At the middle of page 34 of the Brief, Appellant argues that the references are not prior art, as demonstrated by the declaration under 37 C.F.R. §1.131 of all the inventors.

Appellant' argument has been fully considered, but is not deemed to be persuasive and the declaration filed under 37 C.F.R. 1.131 by the inventors Goddard et al. has been considered but is ineffective to overcome the references U.S.Patent No. 6,525,174 and US2002/0110804A1 because the scope of the declaration is not commensurate with the scope of the claims. The instant claims encompass a genus of isolated polypeptides comprising the polypeptide of SEQ ID NO: 14 or its variants. Each of the cited 102 (e) references teach a species of the polypeptide of SEQ ID NO: 14. While the declaration establishes the showing of possession of the polypeptide of SEQ ID NO: 14 and the

nucleic acid sequence of SEQ ID NO: 13, it does not show that Appellant was in possession of the species taught by Young et al. or by Stanton et al. prior to the effective filing date of U.S. Patent No. 6,525,174 or U. S. patent application publication US2002/0110804A1.

Beginning at the middle of page 35 of the Brief, Appellant, citing MPEP and case law, argues that the declaration under 37 C.F.R. §1.131 demonstrates possession of the claimed genus prior to the reference dates. Appellant submits that as described above under Issue III, the disclosed polypeptide of SEQ ID NO: 14 is representative for a genus encompassing its variants.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth at Section III (Rejection of claims 72-76, 83, and 84 under 35 USC § 112, 1st paragraph, written description). It is points out that Appellant was not in possession of the claimed genus of polypeptides at the actual filing date of the instant application, nor before the filing dates of U.S. Patent Application Publication No. 2002/0110804 A1.

At the middle of page 36 of the Brief, Appellant cites the Example 14 of the Written Description Guidelines of the U.S. Patent Office and argues that the claimed polypeptide variants meet the standards set forth in the written description guidelines, standards that demonstrate that Appellants had possession of the claimed genus.

Appellant argues that the declaration demonstrates that Appellant had cloned and sequenced the nucleic acid encoding SEQ ID NO: 14 prior to March 31, 2000. Procedures for making the claimed variant proteins were well known in the art before March 31, 2000. The microarray assay for detecting the recited functional activity of the nucleic acids encoding the claimed polypeptide variants was also known in the art, and as demonstrate by Exhibit B of the declaration. Appellant further submits that the claimed genus of variants possess both the specified functional activity for the encoding nucleic acid, and a defined degree of sequence identity to the SEQ ID NO: 14.

Appellant' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth at Section III (Rejection of claims 72-76, 83, and 84 under 35 USC § 112, 1st paragraph, written description). Moreover, in Example 14 of the Written Description Guidelines of the U. S. Patent Office, the specification exemplifies that a protein of SEQ ID NO: 3 isolated from liver catalyzes the reaction of A→B, and the procedures for making variants of SEQ ID NO: 3 that have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art because deletions, substitutions, insertions, and additions of uncritical amino acid residues would not affect the enzyme activity. Moreover, such an enzyme would have a conserved structure that is responsible for the enzyme activity. Thus, it is likely predictable, based upon percent identity, which variant would share the same function. In contrast, in the instant case the percentage identity is 80%, which is much lower than 95% recited in the Example 14; the recited limitation, "wherein the nucleic acid encoding said polypeptide is

overexpressed in colon, lung or prostate tumor cells", is not sufficiently supported by the specification as noted above; procedures for making variants of SEQ ID NO: 14 which have at least 80% identity to SEQ ID NO: 14 and retains its activity are not conventional in the art because the prior art does not teach that if a single polypeptide or nucleic acid is overexpressed in a certain type of tumor as compared with a normal control, such as colon, lung or prostate tumors, its variants will necessarily be overexpressed.

At the middle of page 37 of the Brief, Appellant argues that the declaration demonstrates that Appellant had cloned and sequenced the nucleic acid encoding SEQ ID NO: 14 prior to December 4, 1998. Procedures for making the claimed variant proteins were well known in the art before December 4, 1998. Appellant submits that the evidence provided in the declaration, together with what was known in the art at the time, suffices to demonstrate that Appellant had possession of the claimed genus including the polypeptide of Young et al. before the December 4, 1998 priority date of Young et al. Appellant' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth immediately above.

At the bottom of page 37 of the Brief, Appellant concludes this section by urging the reversal of the rejections of the claims as anticipated by Young et al. or Stanton et al. under 35 U.S.C. § 102 (e). The Examiner believes that the rejections should be sustained for the reasons set forth above.

At the top of page 38 of the Brief, Appellant concludes their argument by urging reversal of all the outstanding rejections of claims 72-79 and 82-84. The Examiner believes that the rejections should be sustained for the reasons set forth above.

Therefore, for reasons set forth above, Appellant's arguments and evidence have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility, enablement and written description.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted

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